IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Salama et al.	)	Atty. Dkt. 7014-210
	)	
Appl. No.: **National Stage of PCT/DE2004/002762**	)	Examiner: n/a
	)	
Filed: herewith	)	Group Art Unit: n/a

For: Use of CHP as inhibitor of glutathione S transferases and collagen IV

PRELIMINARY AMENDMENT AND FEE AUTHORIZATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please amend the above-identified application as set forth below.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 7 of this paper.

Remarks begin on page 9 of this paper.

Authorization to charge undersigned **deposit account** also appears on page 9.

Amendments to the Specification:

On page 1, between line 4 and 5, directly after the title, please insert the following paragraph:

-- This is the U.S. national stage of International application **PCT/DE2004/002762**, filed December 13, 2004 designating the United States and claiming the benefit of German application DE10359829.4, filed December 12, 2003, which are incorporated herein by reference in their entirety. --

On page 1, please delete line 6.

On page 1, between lines 8 and 9, please insert:

-- FIELD OF THE INVENTION --

On page 1, between lines 16 and 17, please insert:

-- BACKGROUND OF THE INVENTION --

On page 2, between lines 14 and 15, please insert:

-- SUMMARY OF THE INVENTION --

On page 4, please amend the paragraph starting on line 4 as follows:

-- In a preferred fashion, such secondary processes of GST inhibition are associated with other chemical secondary processes of collagen IV inhibition. In particular, the secondary processes of collagen IV inhibition result from the fact that tumor cells dock

via the main collagen domain of this ~~glycolprotein~~ glycoprotein, thus infiltrating and penetrating the cells. However, collagen inhibition not only results in diminished metastasizing and infiltration and invasion in tumor diseases, but also exhibits therapeutic effects in all inflammatory diseases wherein normal tissue is reconstructed into connective tissue, e.g. in lung fibrosis, liver cirrhosis, pancreatic fibrosis and/or glomerulosclerosis. Furthermore, collagen IV inhibition shows a positive influence on scleroderma/Marfan syndrome, vascular diseases, metabolic diseases, autoimmune diseases, and neurological diseases wherein nervous tissue is turned into connective tissue, so-called glioses, as is the case in Alzheimer's disease, for example. In addition to inhibiting collagen IV by CHP, it is obviously possible - particularly in the last-mentioned diseases - to administer parallel medications ~~inducing~~ inhibiting fibrosis, e.g. bleomycin/busulfan, in the form of a supportive/additive therapy. --

On page 6, please amend the paragraph starting on line 2 as follows:

-- (i) Inflammations in the meaning of the invention are reactions of the organism, mediated by the connective tissue and blood vessels, to an external or internally triggered inflammatory stimulus, with the purpose of eliminating or inactivating the latter and repairing the tissue lesion caused by said stimulus. A triggering effect is caused by mechanical stimuli (foreign bodies, pressure, injury) and other physical factors (ionizing radiation, UV light, heat, cold), chemical substances (alkaline solutions, acids, heavy metals, bacterial toxins, allergens, and immune complexes), and pathogens (microorganisms, worms, insects), or pathologic metabolites, derailed enzymes, malignant tumors. The process begins with a brief arteriolar constriction (as a result of adrenaline effect), with inadequate circulation and tissue alteration, followed by development of classical local inflammatory signs (cardinal symptoms, according to GALEN and CELSUS), i.e., from reddening (= rubor; vascular dilation caused by histamine), heat (= calor; as a result of local increase of metabolism), swelling (= ~~tumor~~ turgor; as a result of secretion of protein-rich liquor from vessel walls changed by histamine, among other things, supported by decelerated blood circulation in the sense of a prestasis up to stasis), pain (= dolor; as a result of increased tissue tension and

algogenic inflammation products, e.g. bradykinin), and functional disorders (= functio laesa). The process is accompanied by disorders in the electrolyte metabolism (transmineralization), invasion of neutrophilic granulocytes and monocytes through the vessel walls (cf., leukotaxis), with the purpose of eliminating the inflammatory stimulus and the damaged to necrotic cells (phagocytosis); furthermore, invasion of lymphocyte effector cells, giving rise to formation of specific antibodies against the inflammatory stimulus (immune reaction), and of eosinophiles (during the phase of healing or - at a very early stage - in allergic-hyperergic processes). As a result of the activation of the complement system occurring during the reaction, fragments (C3a and C5a) of this system are liberated which - like histamine and bradykinin - act as inflammation mediators, namely, in the sense of stimulating the chemotaxis of the above-mentioned blood cells; furthermore, the blood coagulation is activated. As a consequence, damage (dystrophia and coagulation necrosis) of the associated organ parenchyma occurs. Depending on the intensity and type of the inflammation, the overall organism responds with fever, stress (cf., adaptation syndrome), leukocytosis and changes in the composition of the plasma proteins (acute-phase reaction), giving rise to an accelerated erythrocyte sedimentation. Preferred inflammations in the meaning of the invention are suppurative, exudative, fibrinous, gangrenescent, granulomatous, hemorrhagic, catarrhal, necrotizing, proliferative or productive, pseudomembranous, serous, specific and/or ulcerous inflammations. --

On page 10, please amend the paragraph starting on line 24 as follows:

-- In another preferred embodiment the cancerous disease or tumor being treated or prophylactically prevented, or whose reappearance is prevented, is selected from the following group of cancerous diseases or tumor diseases ~~comprising cells including the MUC1 in the definition according to the invention, selected from the group of~~: tumors of the ear-nose-throat region, comprising tumors of the inner nose, nasal sinus, nasopharynx, lips, oral cavity, oropharynx, larynx, hypopharynx, ear, salivary glands, and paragangliomas, tumors of the lungs, comprising non-parvicellular bronchial carcinomas, parvicellular bronchial carcinomas, tumors of the mediastinum, tumors of

the gastrointestinal tract, comprising tumors of the esophagus, stomach, pancreas, liver, gallbladder and biliary tract, small intestine, colon and rectal carcinomas and anal carcinomas, urogenital tumors comprising tumors of the kidneys, ureter, bladder, prostate gland, urethra, penis and testicles, gynecological tumors comprising tumors of the cervix, vagina, vulva, uterine cancer, malignant trophoblast disease, ovarian carcinoma, tumors of the uterine tube (Tuba Faloppii), tumors of the abdominal cavity, mammary carcinomas, tumors of the endocrine organs, comprising tumors of the thyroid, parathyroid, adrenal cortex, endocrine pancreas tumors, carcinoid tumors and carcinoid syndrome, multiple endocrine neoplasias, bone and soft-tissue sarcomas, mesotheliomas, skin tumors, melanomas comprising cutaneous and intraocular melanomas, tumors of the central nervous system, tumors during infancy, comprising retinoblastoma, Wilms tumor, neurofibromatosis, neuroblastoma, Ewing sarcoma tumor family, rhabdomyosarcoma, lymphomas comprising non-Hodgkin lymphomas, cutaneous T cell lymphomas, primary lymphomas of the central nervous system, Hodgkin's disease, leukemias comprising acute leukemias, chronic myeloid and lymphatic leukemias, plasma cell neoplasms, myelodysplasia syndromes, paraneoplastic syndromes, metastases with unknown primary tumor (CUP syndrome), peritoneal carcinomatosis, immunosuppression-related malignancy comprising AIDS-related malignancies such as Kaposi sarcoma, AIDS-associated lymphomas, AIDS-associated lymphomas of the central nervous system, AIDS-associated Hodgkin disease, and AIDS-associated anogenital tumors, transplantation-related malignancy, metastasized tumors comprising brain metastases, lung metastases, liver metastases, bone metastases, pleural and pericardial metastases, and malignant ascites. --

On page 12, between lines 7 and 8, please insert:

-- DESCRIPTION OF VARIOUS AND PREFERRED EMBODIMENTS OF THE INVENTION –

On page 15, please delete line 3 and insert therefore:

-- WHAT IS CLAIMED IS: --

Amendments to the Claims:

Please cancel claims 1 to 12 and add claims 13 to 26 as set forth hereinafter.

Listing of Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. to 12. (cancelled)

13. (New) A method for inhibiting collagen IV and/or glutathione S transferase (GST) comprising
administering to cells or a patient benefiting from such inhibition *cis*-hydroxyproline (CHP) in a collagen IV and/or glutathione S transferase (GST) inhibiting effective amount.

14. (New) The method of claim 13, wherein said inhibition is effected *in vitro* or *in vivo*.

15. (New) The method of claim 13, wherein CHP is in form of a gel, poudrage, powder, tablet, sustained-release tablet, premix, emulsion, brew-up formulation, infusion solution, drops, concentrate, granulate, syrup, pellet, bolus, capsule, aerosol, spray and/or inhalant.

16. (New) The method of claims 13, wherein a formulation comprising CHP at a concentration of from 0.1 to 99.5 wt.% is administered.

17. (New) The method of claims 16, wherein a formulation comprising CHP at a concentration of from 0.5 to 95 wt.% is administered.

18. (New) The method of claims 17, wherein a formulation comprising CHP at a concentration of from 1 to 80 wt.% is administered.

19. (New) The method of claim 15, wherein CHP is in form of a infusion solutions having a

concentration of 1 to 2 wt.% of CHP.

20. (New) The method of claims 13, wherein CHP is administered at amounts of from 0.05 to 1000 mg per kg body weight per 24 hours.

21. (New) The method of claims 20, wherein CHP is administered at amounts of from 5 to 450 mg per kg body weight per 24 hours.

22. (New) A method for the inhibition of glutathione S transferase and/or collagen IV in an *in vivo* or *in vitro* system, wherein the system is contacted with CHP.

23. (New) The method of claim 22, wherein the system is an *in vivo* systems and contacting is effected orally, vaginally, rectally, nasally, subcutaneously, intravenously, intramuscularly, regionally, intraperitoneally and/or topically.

24. (New) An anti-collagen IV and/or anti-GST agent comprising CHP, optionally together with a pharmaceutically tolerable carrier, wherein said agent inhibits collagen IV and/or GST.

25. (New) The agent of claim 24, wherein the carrier is a filler, diluent, binder, humectant, disintegrant, dissolution retarder, absorption enhancer, wetting agent, adsorbent and/or lubricant.

26. (New) The agent of claim 24, wherein said carrier is a liposome, siosome and/or niosome.

Remarks

Claims 1 to 12 have been cancelled and claims 13 to 26 have been added so that claims 13 to 26 are pending in this application of which claim 13, 22 and 24 are in independent form. The above claim amendments and additions are made to eliminate improper multi-dependencies under U.S. practice and to rewrite "use" claims so as to place the claims in form consistent with 37 CFR 1.75 (c) in order to ensure examination of such claims.

The amendments and additions are not "narrowing." The scope of the claims has not been reduced; no new limitations have been added and none are intended.

The disclosure has been amended to add appropriate headings. Several typographical errors in the specification have been amended. Applicant submits that these errors constitute obvious errors and do not add any new matter.

The Commissioner is authorized to charge any deficiencies in fees to avoid abandonment of this national stage application and overpayments to deposit account number 50-3135.

Respectfully submitted,

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